SECURITY CLASSIFICATION OF

AD-A261 258

PAGE

1a. REPORT SECURITY CLASSIFICATION: Unclassified	TIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY: N/A	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE: N/A	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S): AFOSR-TR- 93 0068
6a. NAME OF PERFORMING ORGANIZATION: Mississippi State University	6b. OFFICE SYMBOL (If applicable)
7a. NAME OF MONITORING ORGANIZATION: AFOSR	
6c. ADDRESS (City, State and ZIP Code): College of Veterinary Medicine, P.O. Drawer V, Mississippi State, MS 39762	7b. ADDRESS (City, State and ZIP Code): 110 Duncan Ave Suite B116 BAFB DC 20332-0001
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: AFOSR	8b. OFFICE SYMBOL (If applicable): NL
9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: AFOSR-91-0338	
8c. ADDRESS (City, State and ZIP Code): Bolling Air Force Base, DC 20332-6448	10. SOURCE OF FUNDING NOS.

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT NO
61102F	2312	AS	

11. TITLE (Include Security Classification): Quantitative Structure-Activity Relationships of Chlorinated Alicyclic Compounds

12. PERSONAL AUTHOR(S): Chambers, Janice Elaine

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Yr., Mo., Day)	15. PAGE COUNT
Annual	FROM 01/01/92 TO 31/12/92	1993 January 31	12

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB. GR.	Chlorinated alicyclic compounds QSAR GABA receptors

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The project, which was designed to conduct a quantitative structure-activity relationship study on a series of chlorinated alicyclic compounds (a number of which are insecticides or their metabolites or degradation products) was initiated, with the neurochemical characterization being conducted at Mississippi State University and the physicochemical characterization being conducted at Iowa State University. Experiments quantified the inhibitory potency of the compounds for the binding of ^{35}S-t-butylbicyclophosphorothionate (TBPS), which binds to the γ-aminobutyric acid (GABA) receptor, the target for the test compounds. A wide range of potencies were discovered (IC50's of 4.2-22,734 nM), which correlated well with acute toxicity levels. NMR analysis of the compounds has been run and the molecular connectivity calculations have been initiated.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS ☐	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE NUMBER (Include Area Code)	22c. OFFICE SYMBOL
Dr. Walter J. Kozumbo	202-767-5021	NL

DD FORM 1473, 83 APR EDITION OF 1 JAN 73 IS OBSOLETE.

SECURITY CLASSIFICATION OF THIS PAGE

Report 91-0338

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS OF CHLORINATED ALICYCLIC COMPOUNDS

Janice E. Chambers
College of Veterinary Medicine
Mississippi State University
P.O. Drawer V
Mississippi State, MS 39762

31 January 1993

Annual Report for Period 1 January 1992 - 31 December 1992

ANNUAL TECHNICAL REPORT

STATEMENT OF WORK

A quantitative structure-activity relationship study will be performed on 33 chlorinated alicyclic compounds, most of which are chlorinated cyclodiene insecticides or their structural analogs. Their action at the t-butylbicyclophosphorothionate (TBPS) binding site of the γ-aminobutyric acid (GABA) receptor/Cl^- ionophore complex will be correlated with their lipophilicity, electronegativity and/or molecular connectivity characteristics.

The two biological parameters will be investigated at Mississippi State University. The in vitro potency of the test compounds to compete with [^{35}S]TBPS for binding to rat brain membranes will be studied. Also, the potency of the test compounds to inhibit $^{36}Cl^-$ flux into rat brain vesicles will be studied.

The three chemical parameters will be investigated at Iowa State University. Nuclear magnetic resonance will be used to evaluate the electronic character of the alicyclic hydrocarbons to be studied. Partition coefficients will be determined for the series of chemicals. Topological characteristics will be elucidated using molecular connectivity indices.

STATUS OF THE RESEARCH

The project, which is designed to conduct a quantitative structure-activity relationship study on a series of chlorinated alicyclic compounds (a number of which are insecticides or their metabolites or degradation products) investigated neurochemical parameters at Mississippi State University and physicochemical parameters at Iowa State University. Experiments were conducted which quantified the potential interaction of the test compounds for the γ-aminobutyric acid (GABA) receptor for the binding of ^{35}S-t- butylbicyclophosphorothionate (TBPS) to rat brain membranes. The rat brain membranes bound TBPS with a Kd of 24.6 nM, which compares favorably with what is reported from the other labs in the literature (Figs. 1 and 2). All but one of the compounds were inhibitory, and they displayed a wide range of potencies, with IC_{50}'s of from 4.22-22,734 nM (Table 1, Fig. 3 A-D). The IC_{50}'s correlated well with published rat oral acute toxicity values (Table 1, Fig. 4). The $^{36}Cl^-$ flux experiments will be initiated shortly.

The EPSCoR graduate student supplement has been initiated, starting with a characterization of ^{35}S-TBPS binding to catfish brain membranes.

Purities of the compounds have been checked, and nuclear magnetic resonance analysis has been concluded. Information on structures has been entered to initiate the molecular connectivity calculation.

PUBLICATIONS

Ma, T., J. Tang and J.E. Chambers. 1992. The relationship of the neurochemical actions of chlorinated alicyclic compounds to acute toxicity. Society of Environmental Toxicology and Chemistry Abstracts, WA6G8, p. 228.

Above paper was also presented to the South Central Chapter of the Society of Toxicology meeting, and the abstract was published in the meeting program.

PERSONNEL

Mississippi State University

Janice E. Chambers, Ph.D., Principal Investigator
Tangeng Ma, Ph.D., Postdoctoral Associate
Jun Tang, B.S., Graduate Student
Russell Carr, M.S., Graduate student (EPSCoR supplement)

Iowa State University

Joel R. Coats, Ph.D., Co-Investigator
Jian bo Liu, M.S., Graduate student

INTERACTIONS

None.

NEW DISCOVERIES

None.

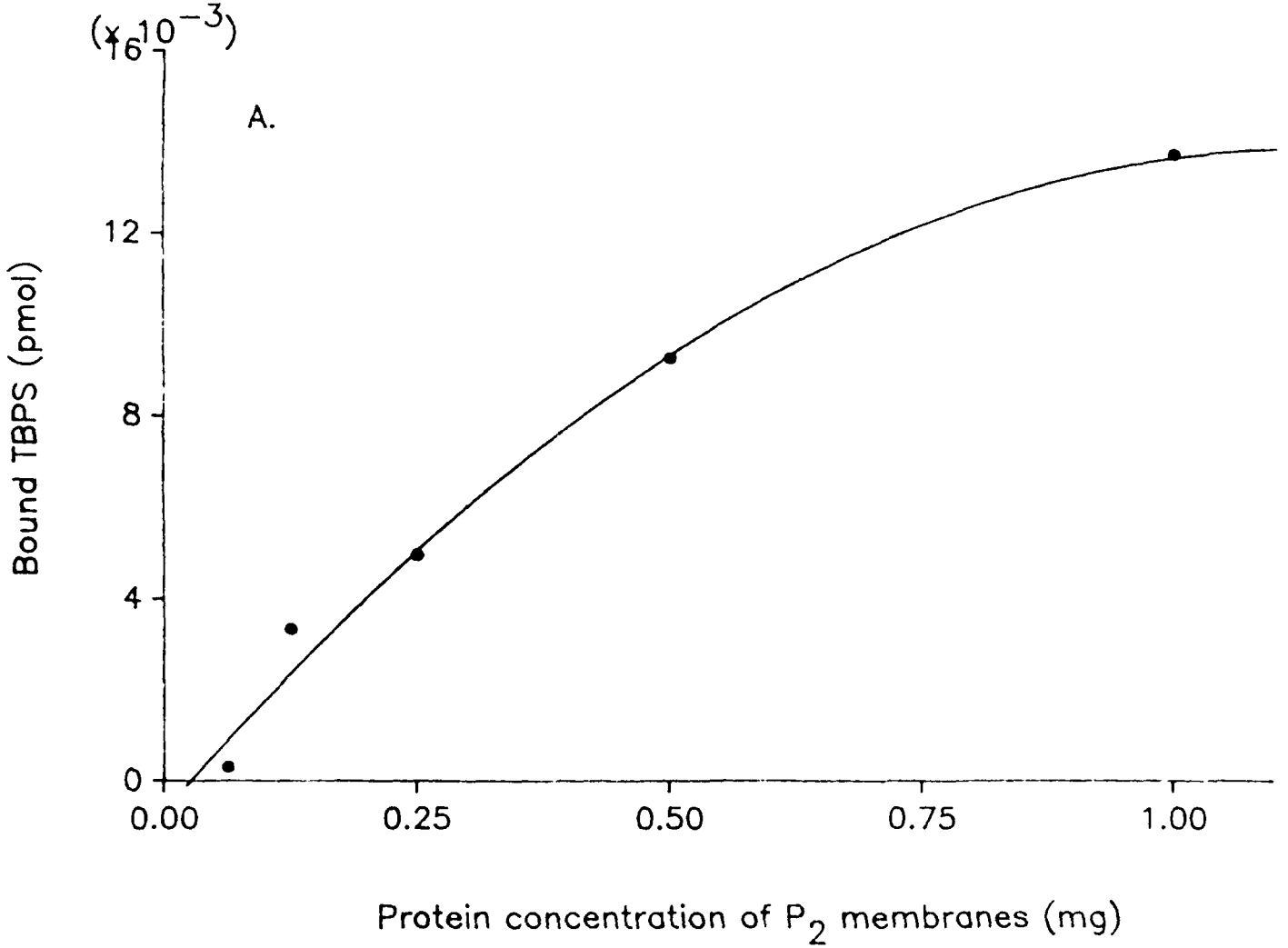
OTHER INFORMATION

This report covers months 7-18, the first half of the project. Half of the neurochemical and physicochemical research has been conducted. The EPSCoR supplement has been initiated. Work is progressing steadily at this point.

Table 1. The inhibitory potencies of chlorinated alicyclic compounds for ^{35}S-t-butylbicyclophosphorothionate binding to rate brain membranes.

	IC_{50} (nM)	LD_{50} (mg/kg)
Aldrin	319 ± 42	39-60
Dieldrin	158 ± 51	46
Isodrin	28.9 ± 5.4	7 - 16
Endrin	16.9 ± 5.1	8 - 18
Telodrin	31.2 ± 18.3	3 - 10
Aldrin trans-diol	13,564 ± 1,163	
Aldrin cis-diol	8,778 ± 886	
Dihydroaldrin	140 ± 60	
9-Ketoendrin	11.6 ± 2.4	
12-Ketoendrin	4.22 ± 0.42	
Dihydroisodrin	48.0 ± 7.2	
Heptachlor	302 ± 99.3	100 - 162
Heptachlor epoxide	61.4 ± 29.1	47 - 61
Photoheptachlor	4.23 ± 1.00	
Photoheptachlor epoxide	5.26 ± 0.82	
Photo α-chlordane	52.3 ± 14.7	
Oxychlordane	36.6 ± 20.1	
Photooxychlordane	29.2 ± 5.3	
Chlordene	2,577 ± 484	
Photochlordene	210 ± 71	
1-Hydroxychlordene	4,449 ± 538	2,400 - 4,600
Dihydrochlordene	1,660 ± 197	
2,3-Chlordene epoxide	334 ± 70	
1,2,3,4,9,9-Hexachloro-1,4,4a,5,6,8a-hexahydro-1,4-methanonaphalene	737 ± 294	
1,2,3,4,9,9-Hexachloro-1,4,4a,5,6,8,8a-octahydro-1,4-methanonaphalene	574 ± 287	
5,6,7,8,9,9-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-ethano-5,8-methanonaphalene	56.6 ± 13.0	
5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-2,3-epoxy-1,4-thano-5,8-methanonaphalene	145 ± 44	
5,6,7,8,9,9-Hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4-ethano 5,8-methanonaphalene	131 ± 14.7	
Mirex	"No inhibition"	600 - 740
Chlordecone (Kepone)	22,734 ± 6,674	125
Lindane (γ-BHC)	203 ± 41	88-91

Fig. 1: Binding of ^{35}S-TBPS to rat brain membranes.



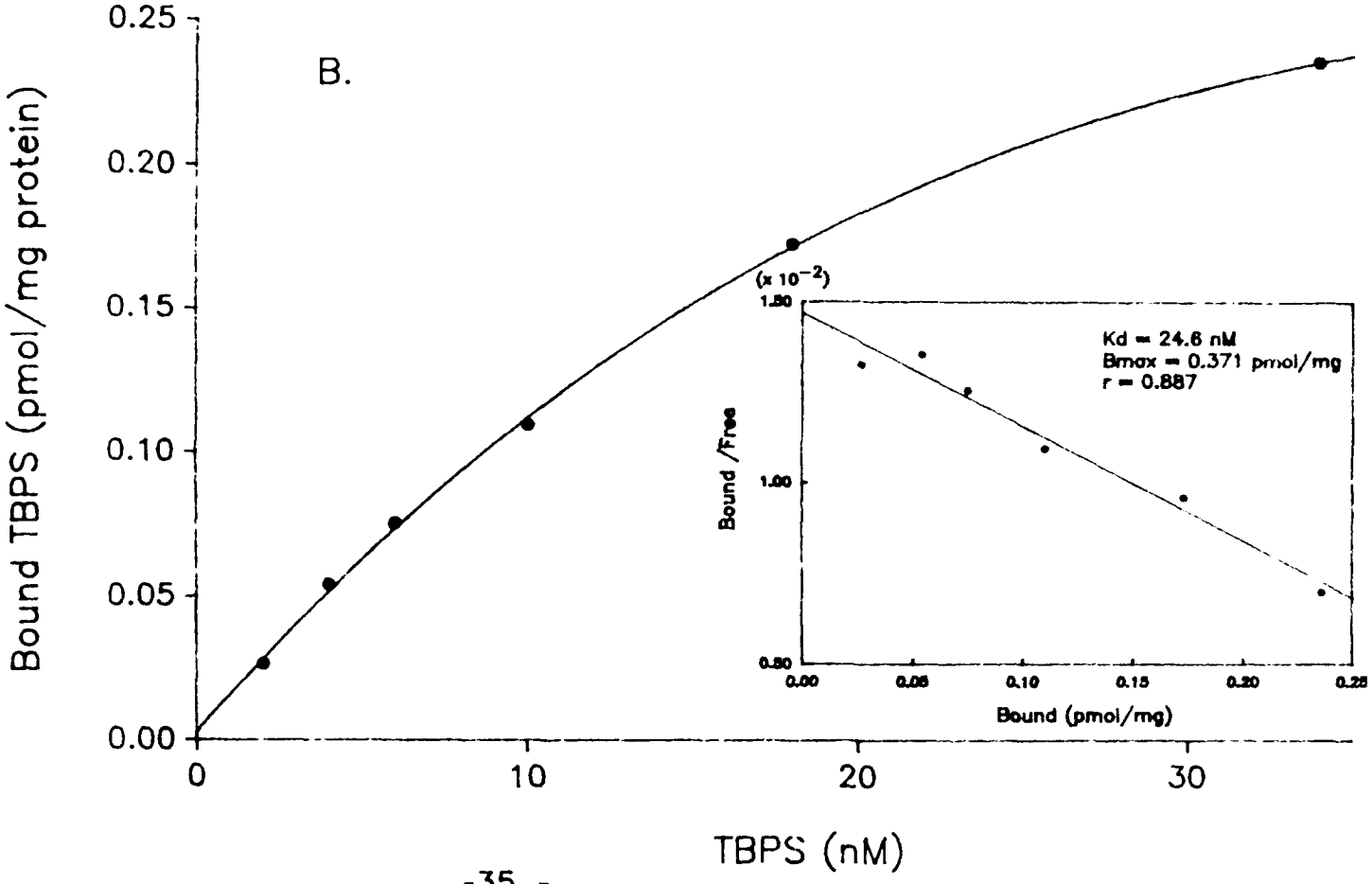
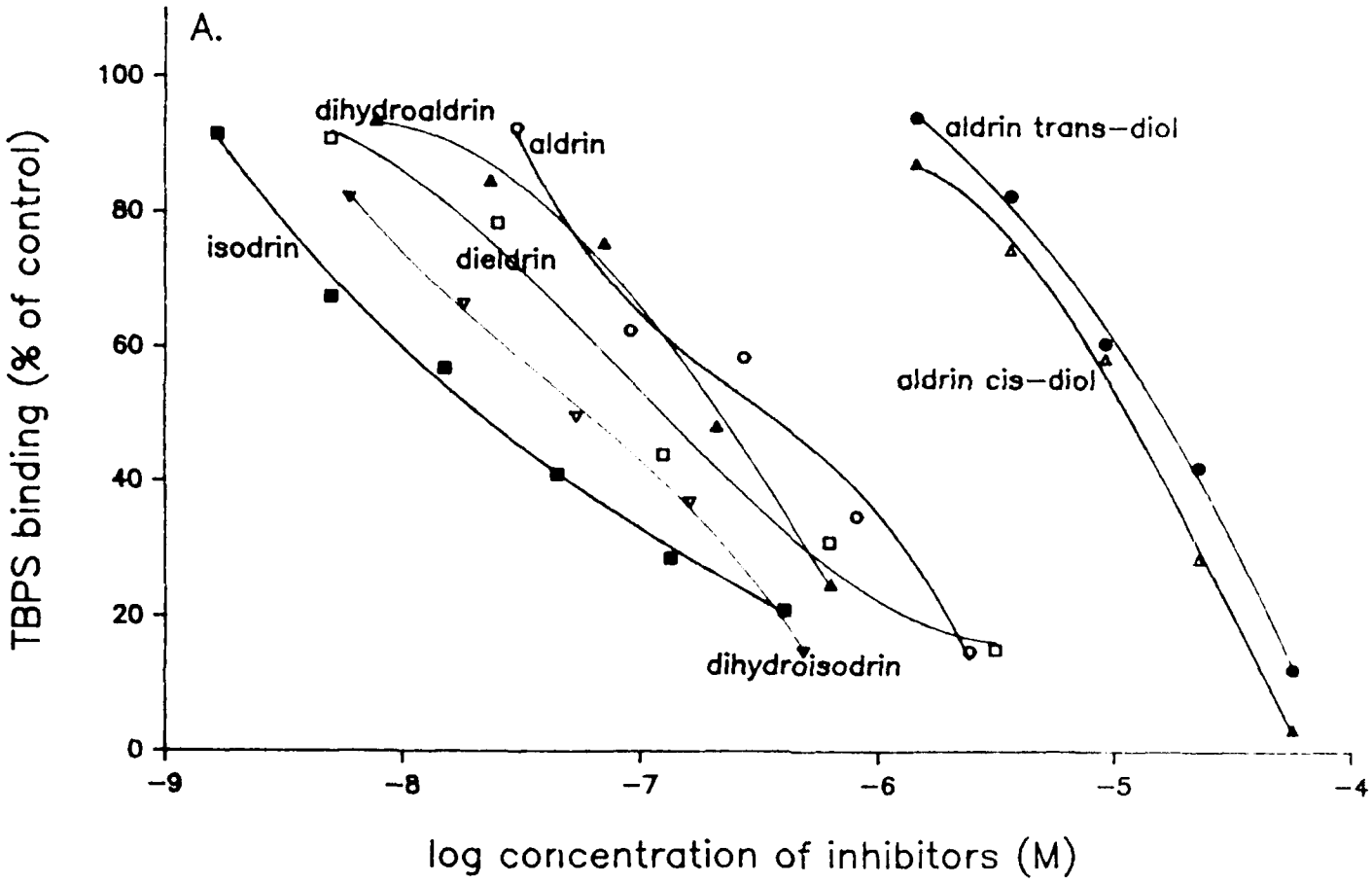
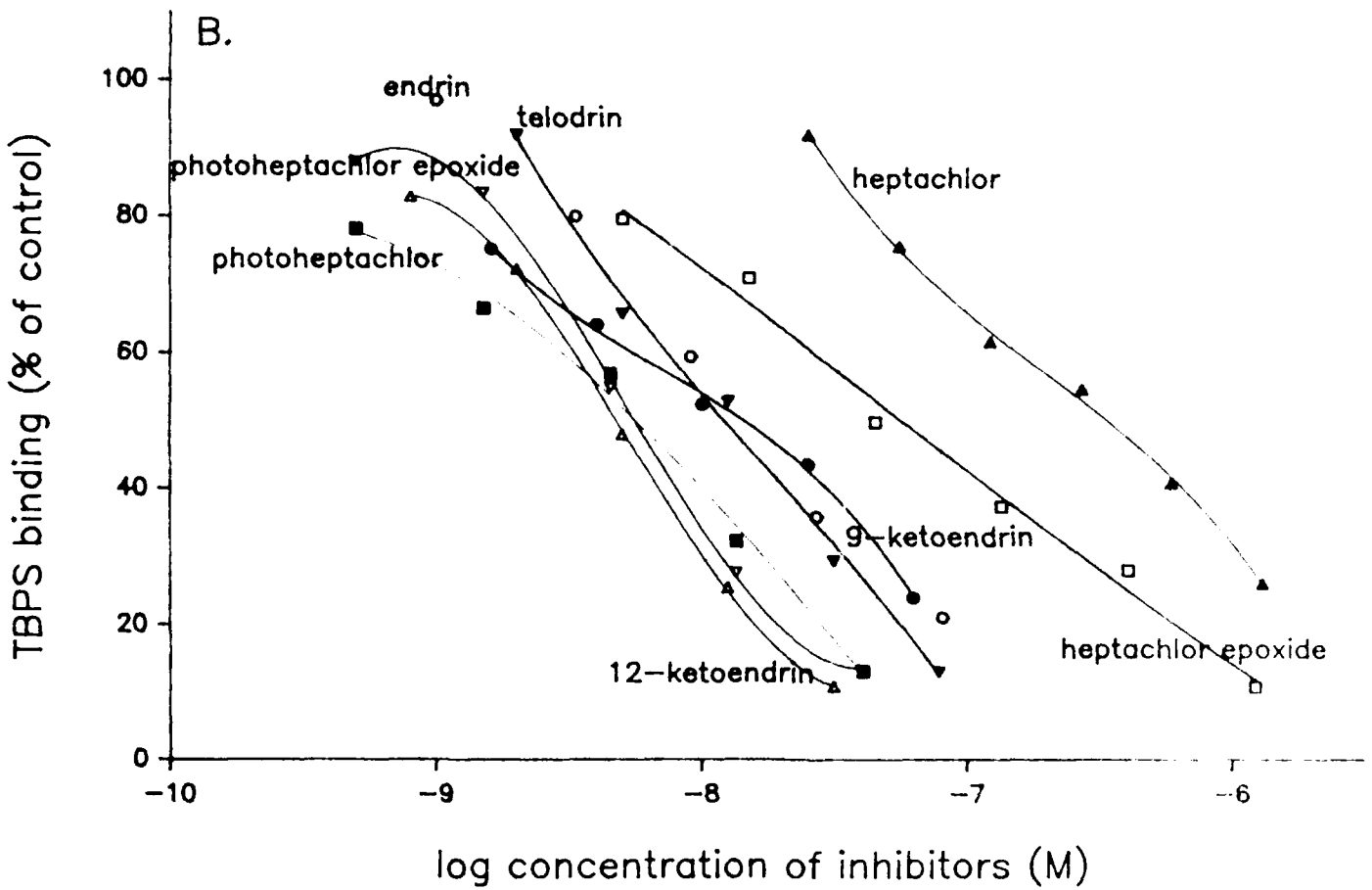
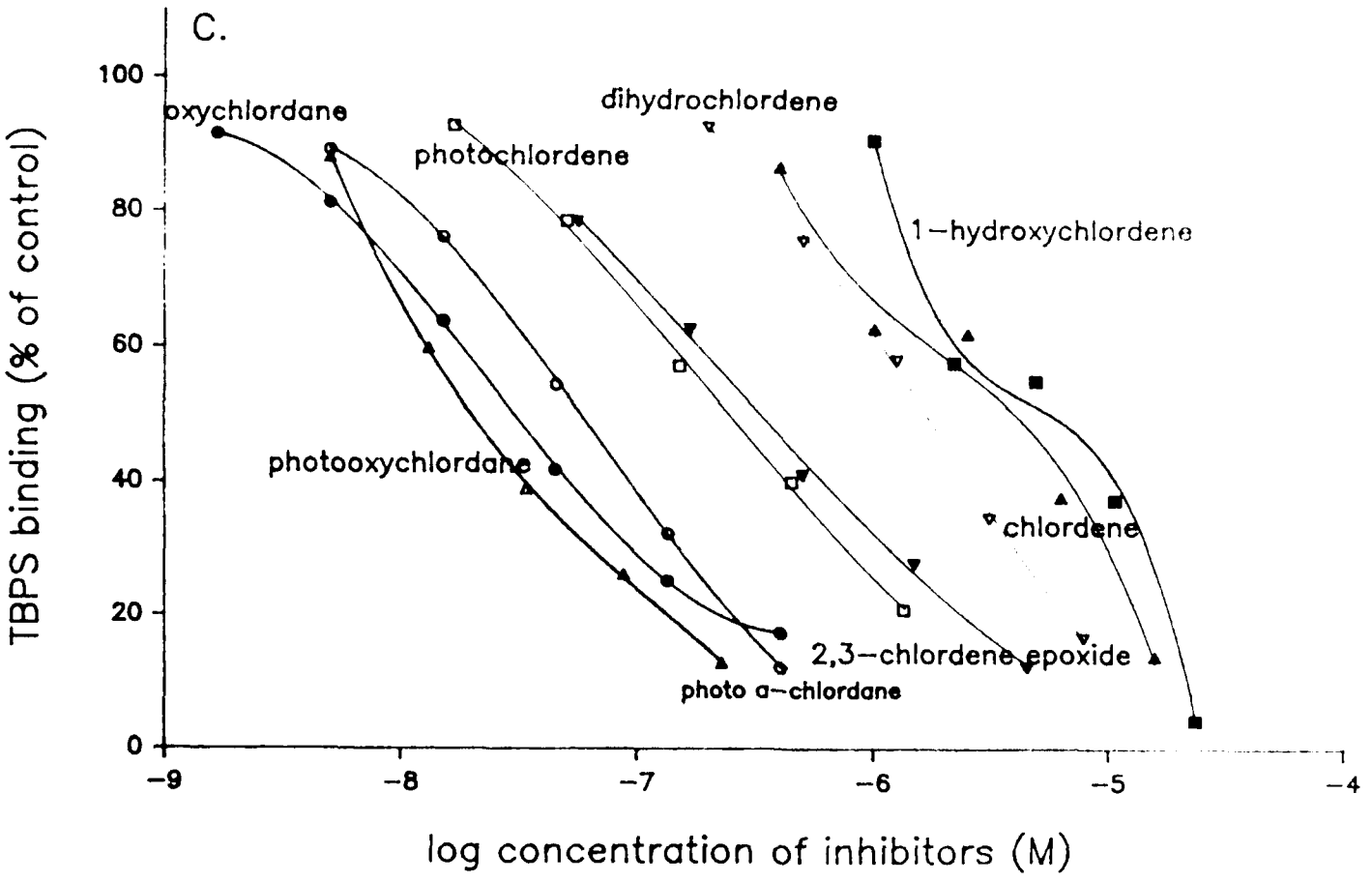


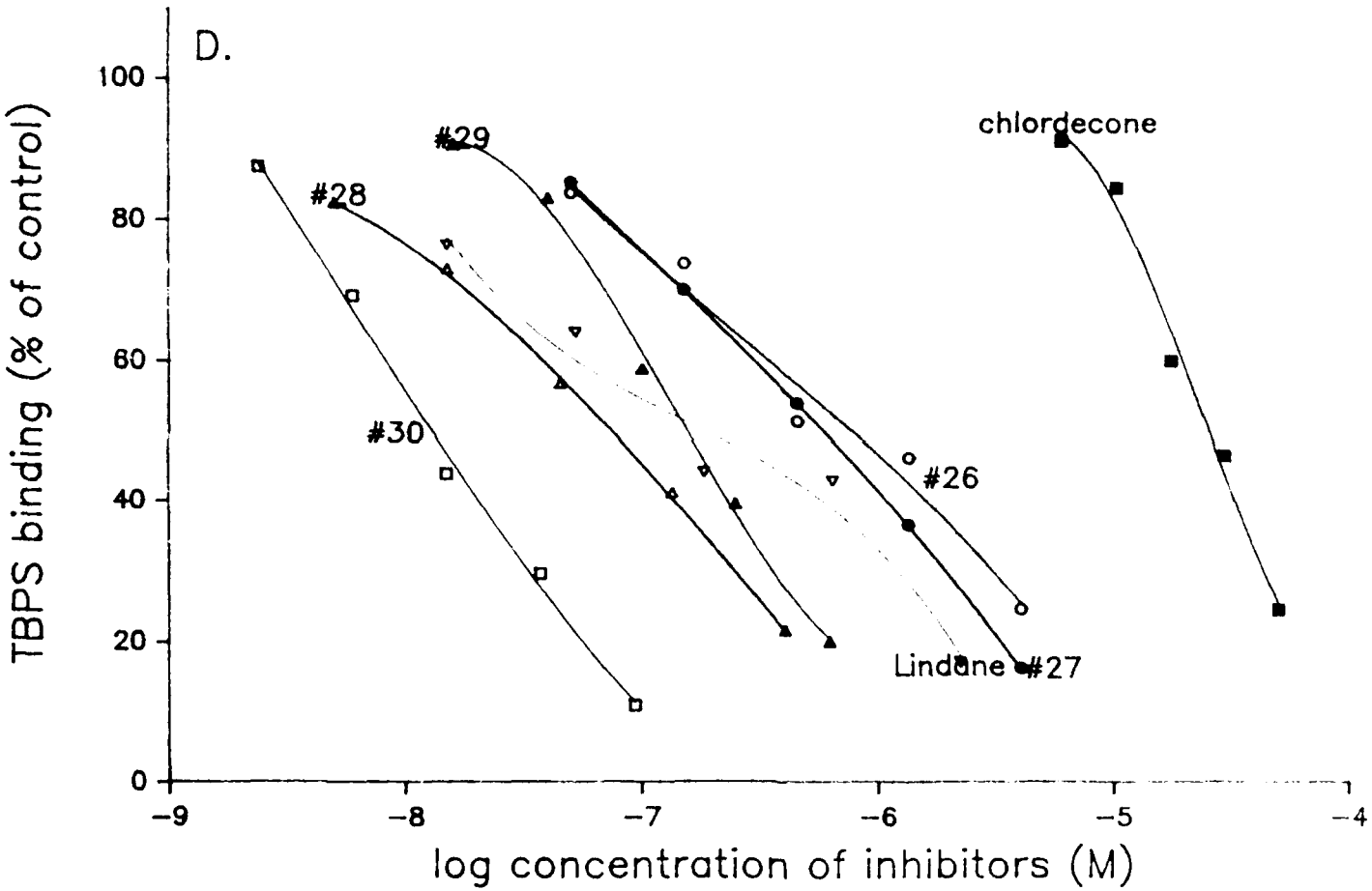
Fig. 2. Specific binding of [^{35}S]TBPS to P_2 membranes from rat brain.
A: as a function of P_2 membrane concentrations.
B: a saturation curve; Inset show Scatchart transformation of the data.

Fig. 3, A-D. Competition of chlorinated alicyclic compounds for ^{35}S-TBPS binding to rat membranes.




B.
endrin
telodrin
photoheptachlor epoxide
photoheptachlor
heptachlor
9–ketoendrin
heptachlor epoxide
12–ketoendrin
TBPS binding (% of control)
100
80
60
40
20
0
−10
−9
−8
−7
−6
log concentration of inhibitors (M)


C.
100
80
60
40
20
0
TBPS binding (% of control)
oxychlordane
photochlordene
dihydrochlordene
1–hydroxychlordene
photooxychlordane
chlordene
2,3–chlordene epoxide
photo α–chlordane
–9
–8
–7
–6
–5
–4
log concentration of inhibitors (M)


D.
TBPS binding (% of control)
100
80
60
40
20
0
#29
#28
#30
chlordecone
#26
Lindane
#27
−9
−8
−7
−6
−5
−4
log concentration of inhibitors (M)

#26: 1,2,3,4,9,9-hexachloro-1,4,4a,5,6,8a-hexahydro-1,4-methanonaphalene.
#27: 1,2,3,4,9,9-hexachloro-1,4,4a,5,6,8,8a-octahydro-1,4,-methanonaphalene.
#28: 5,6,7,8,9,9-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-ethano-5,8-methanonaphalene.
#29: 5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8,8a-octahydro-2,3-epoxy-1,4-thano-5,8-methanonaphalene.
#30: 5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4-ethano-5,8-methanonaphalene.

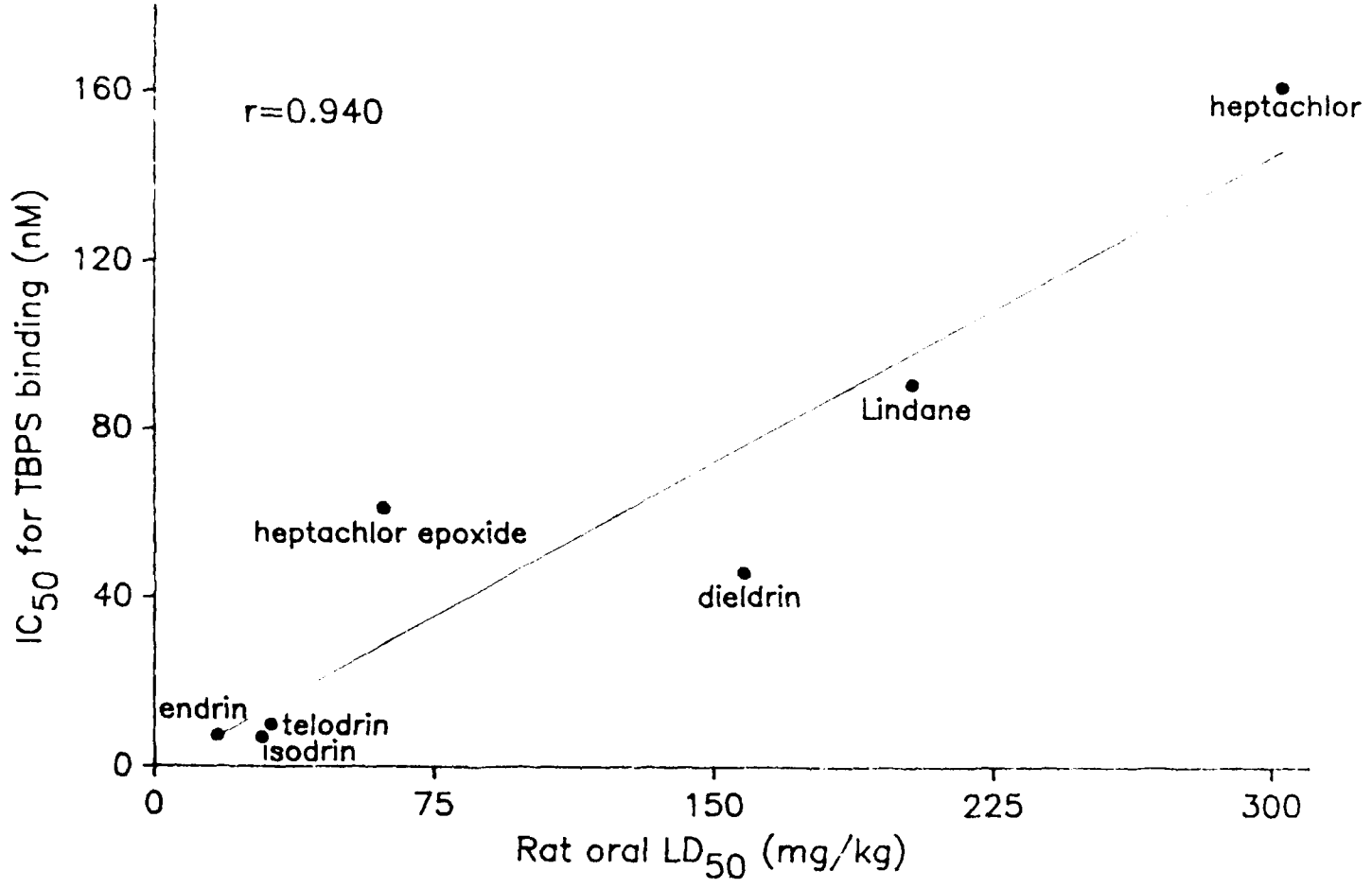


Fig. 4. Correlation by least squares linear regression of inhibitory potency in TBPS binding assays with acute oral toxicity in female rats for chlorinated alicyclic compounds.